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The identification of common haplotypes on bovine chromosome 5 within commercial lines of *Bos taurus* and their associations with growth traits[1]

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ABSTRACT: The cosegregation between a genetic marker and the QTL in a well-designed mapping population is the basis for successful QTL mapping. Linkage disequilibria are, however, also expected among individuals that descended from the same breeding line, and some common haplotypes should carry on and segregate among individuals of the line. These identical by descent haplotypes make it possible to identify and locate the QTL segregating in the line. We report the identification of common haplotypes within commercial lines of *Bos taurus* and their associations with growth traits. One hundred and seventy six male calves and their 12 sires (9 to 30 male calves of each sire) of the Beefbooster, Inc., M1 line selected for maternal traits over 30 yr were genotyped using 16 microsatellite markers chosen from bovine chromosome 5 for the initial haplotype and growth association analysis. In order to verify the results from the M1 line, another 170 male calves and their 14 sires from the Beefbooster M3 line were genotyped using nine microsatellite markers chosen from bovine chromosome 5. The alleles of each male calf contributed by the sire and by the dam were identified, and haplotypes in the M1 line were established along 93% of bovine chromosome 5. The haplotypes in the M3 line were established along the chosen regions of bovine chromosome 5. Regression analysis detected 10 haplotypes in three chromosomal regions (0 to 30 cM, 55 to 70 cM, and 70 to 80 cM) that showed significant associations with birth weight, preweaning average daily gain, and average daily gain on feed in M1 line and 9 haplotypes associated with the growth traits in the same chromosomal regions in the M3 line at the comparisonwise threshold level. On average, the 19 haplotypes have an effect of 0.68 SD on the growth traits, ranging from 0.41 SD to 1.02 SD The results provide a useful reference for further positional candidate gene research and marker-assisted selection.

Key Words: Cattle, Haplotypes, Quantitative Traits

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Introduction

Identification and mapping of QTL for growth and carcass traits in beef cattle have recently been reported in a number of studies (Davis et al. 1998; Stone et al. 1999; Casas et al. 2000). Davis et al. (1998) detected and mapped five QTL for birth weight on bovine chromosome (**BTA**) 5, 6, 14, 18, and 21 in three Charolais × Brahman paternal half-sib families. Elo et al. (1999) detected a QTL for live weight on BTA23. Stone et al. (1999) reported significant evidence of QTL on BTA 1, 2, 5, and 13, with suggestive evidence of QTL on BTA 7, 11, 14, 18, and 26 that affect carcass and growth traits in a Brahman paternal half-sib family. A study by Casas et al. (2000) suggested that QTL were segregating in regions of BTA 5, 6, 7, 13, 14, 17, 19, 22, 27, and 29 for carcass composition and growth in a Piedmontese paternal half-sib family and in a Belgian Blue family.

Fine mapping of QTL is necessary to provide a useful reference for further candidate gene research that may eventually lead to the identification of the causative genes. Such fine mapping approaches, especially for a QTL with a small effect, usually require a large sample size in a well-designed mapping population. Obtaining such populations is costly and may be impractical in commercial herds. It is expected, however, that individuals within a semi-closed population, such as a commercial line of cattle, may be derived from one or a limited

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number of founders. Thus, some common haplotypes originating from the common ancestors may carry on and segregate among individuals of the breeding line, particularly when selection is applied. These common haplotypes may harbor QTL of interest and make it possible to locate QTL segregating in the line. The theoretical basis for this method, identity by descent haplotype sharing, which can exploit the historical recombinants rather than generate new ones, is described in detail elsewhere (Donnelly, 1983; Lander and Botstein, 1986; de Vries et al. 1996). We report the identification of common haplotypes within lines of *Bos taurus* and their associations with growth traits using genetic markers of BTA5, a chromosome which has had QTL for growth identified in a number of studies (Davis et al. 1998; Stone et al. 1999; Casas et al. 2000).

Materials and Methods

Animals and Phenotypic Data

Animals were from the M1 and M3 lines of Beefbooster, Inc. The M1 line was developed from an Angus base and is a medium-framed, maternal strain selected for fertility, mothering ability, and preweaning gain. The M3 line is small-framed, maternal strain developed from small cows of various breeds that have no difficulty calving. The selection criteria for the M1 and M3 lines are based on indices described by MacNeil and Newman (1994). A 10-mL blood sample was collected by venipuncture from each male calf and potential sire. The DNA from each blood sample was extracted for later parentage identification. Sire identification was carried out by the Saskatchewan Research Council using DNA microsatellite markers. The male calves were weaned and weighed in the fall of 1998, and over one-third (38.6%) of the bull calves with the lowest preweaning gain were culled. The remaining male calves were placed in feedlot pens for postweaning performance testing. The date and weight when feeding commenced, as well as the date and weight when feeding was finished, were recorded for each male calf.

Genotyping and Haplotype Identification

One hundred and seventy-six male calves and their 12 sires (9 to 30 calves of each sire) of the M1 line were genotyped using 16 microsatellite markers chosen from BTA 5. The sixteen loci are ILSTS42, BM6026, BP1, BL23, ILSTS22, CSSM34, RM500, BR2936, BMS490, ETH10, IGF-1, BM1819, RM29, BMS1248, BM315, and BM2830, which span approximately 114 cM, or 93% of the chromosome. Genotypes of each male calf were checked against the calf's sire to verify the sire inheritance. Alleles contributed by the sire as well as by the dam were identified for each calf by examining the genotype of the calf's sire. The haplotypes (allele linkage phases) of the calf were then established along BTA5. In order to verify the QTL regions identified in the M1 line, another 170 male calves and their 14 sires (5 to 29 calves of each sire) from another commercial line, the Beefbooster M3 line, were also genotyped using nine microsatellite markers chosen from bovine chromosome 5. The nine microsatellite markers spanned the haplotypes associated with the growth traits in the M1 line and are BM6026, BP1, BL23, RM500, BR2936, BMS490, IGF-1, BM1819, and RM29. The identities of alleles of each locus in M3 line were decided using samples of M1 line as a reference and the haplotypes of the calf in M3 line were determined the same way.

Statistical Analysis

The general linear model of SAS (SAS Inst. Inc., Cary, NC) was used to test the association between a haplotype and the growth traits. The linear model for M1 line was $Y_{ijk} = \mu + H_i + G_j + (HG)_{ij} + A_k + E_{ijk}$, where Y_{ijk}= the observation of the i^{th} haplotype under the j^{th} herd effect and k^{th} dam effect; μ = overall experimental mean; H_i = haplotype type effect, taking 1 when the individual has the haplotype or 0 when the individual is without the haplotype or the haplotype cannot be established; G_j = herd effect, taking 1 or 2 as only two herds used; $(HG)_{ij}$ = interaction between haplotype and herd; A_k = dam age effect, taking 1 if the dam age ≤ 6 yr of age, 2 if the dam age >6 and <9 yr of age or 3 if the dam age ≥ 9 yr of age; and E_{ijk}= residual error. The dam age was treated as a class variable with the three levels based on the plotting of dam age against the growth traits, in which the dam ages could be classified into three distinct levels and each level of dam age had a similar effect on growth traits. The linear model for M1 line was a reduced model with the herd effect Gj and haplotype × herd interaction effect $(HG)_{ij}$ removed, because the animals in M3 line were from only one herd.

Haplotype effect, herd effect and dam age effect were all treated as fixed effects. Type III sum of squares was used in all *F*-tests. The analyses were performed between the most commonly observed haplotypes and birth weight (**BWT**), preweaning average daily gain (**PWADG**), and average daily gain on feed (**ADGF**) using the SAS general linear model analysis, in which the difference between animals with the haplotype and without the haplotype or with uncertain haplotypes was tested. A complete dominance effect of the haplotype was assumed, in which animals carrying one copy of the haplotype and animals carrying two copies of the haplotype were treated the same. The summary statistics of the three growth traits, BWT, PWADG, ADGF, in M1 and M3 lines are presented in Table 1.

The comparisonwise and chromosomewise thresholds of *P*-value were generated empirically from the permutation method outlined by Churchill and Doerge (1994) for each trait of each line. Briefly, the individuals were indexed from 1 to n. The trait data were then randomly shuffled. The shuffled data were also indexed from 1 to n and assigned back to the individual with the same index. The new data set with randomly shuf-

Table 1. Summary statistics of growth traits in M1 and M3 lines of *Bos taurus* from Beefbooster, Inc.

Line and Trait[a]	Mean	Rnge	SD[b]
		M1	
BTW, kg	41.35	27.24–52.66	4.48
PWADG, kg	1.15	0.87–1.53	0.11
ADGF, kg	1.33	0.48–1.94	0.18
		M3	
BTW, kg	29.42	21.34–43.13	3.98
PWADG, kg	0.95	0.72–1.23	0.10
ADGF, kg	1.09	0.22–1.34	0.14

[a]BTW = birth weight, PWADG = preweaning average daily gain, ADGF = average daily gain on feed. [b]S.D. = standard deviation.

fled trait data was analyzed again for all common haplotypes along BTA 5 and the corresponding *P*-values were stored. The entire procedure was repeated 1,000 times. The comparisonwise threshold of *P*-value for a given haplotype was calculated by choosing $100(1-\alpha)$ percentile (α is the type I error) of its *P*-value distribution. The $100(1-\alpha)$ percentile of the 1,000 lowest *P*-values of each chromosome scan for a given growth trait was selected as the empirical chromosomewise threshold for that trait. Type I errors of 0.05 and 0.10 were used for calculating comparisonwise and chromosomewise *P*-value thresholds respectively. Once the associations between haplotypes and the growth traits were determined, Pearson correlation coefficients among haplotypes associated with the growth traits at or close to the chromosomewise significance level were examined. The permutation and correlation analyses were performed also using SAS (SAS Inst. Inc.).

Results

Common Haplotypes in the M1 Line and Their Associations with Growth Traits

On average, 5.9 alleles were detected for each locus of BTA 5 in the M1 line, with a range of 2 to 10 alleles per locus. A haplotype is defined by alleles at adjacent loci along BTA 5. For loci ILSTS42 and BM6026, the haplotype 8-6 represents a segment of chromosome having allele 8 at ILSTS42 (ILSTS42-8) and allele 6 at BM6026 (BM6026-6). It was found that haplotypes across two adjacent loci appeared to be in higher frequencies than haplotypes that span more than two loci. The frequencies of the most common haplotype ranged from 8.0% (haplotype 2-4 of BMS490 and ETH10) to 47.2% (haplotype 2-5 of IGF-1 and BM1819), with an average of 19.96%.

Associations between a haplotype and the growth traits were analyzed only for the most common haplotypes, which were exclusively haplotypes of adjacent loci. Figure 1 depicts the haplotypes with the lowest *P*-values between two adjacent loci along BTA 5 for the

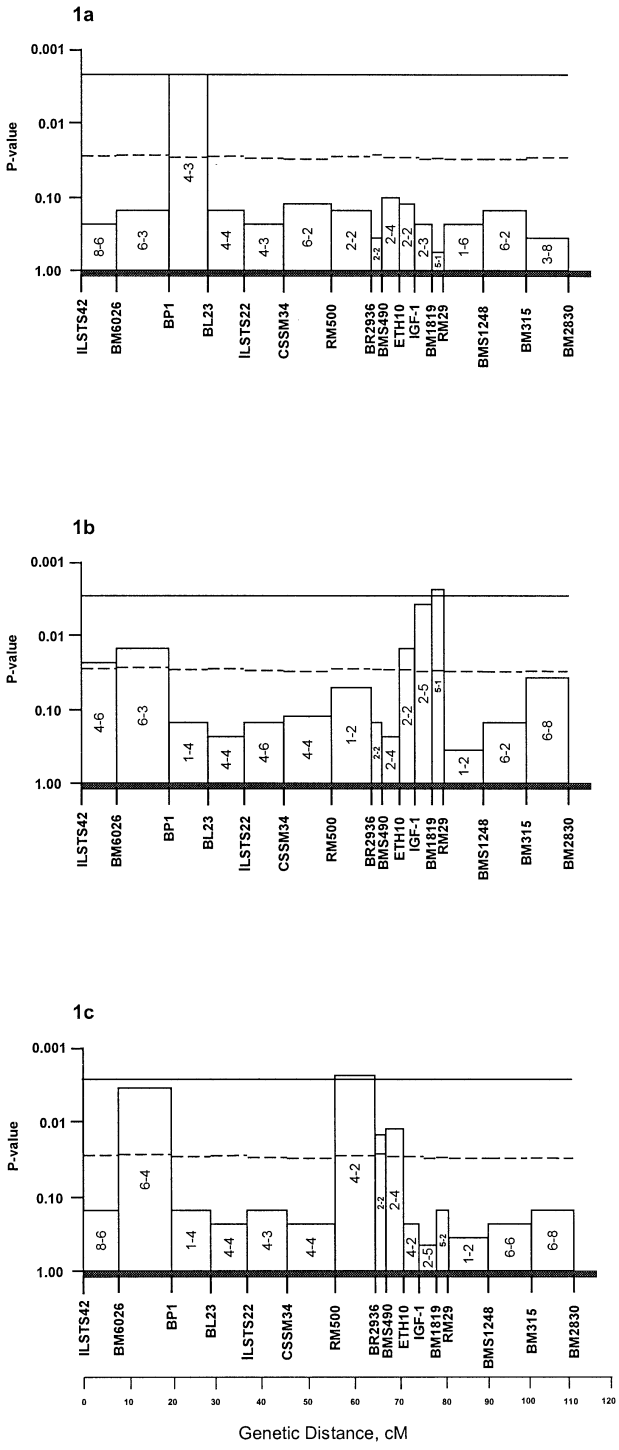

Figure 1. Haplotypes with the lowest *P*-values between two adjacent loci along BTA5 for birth weight (1a), preweaning average daily gain (1b), and average daily gain on feed (1c) in M1 line. Haplotypes were defined by two alleles of a pair of loci. For example, haplotype 8-6 of locus pair ILSTS42 and BM6026 represents a segment of chromosome having allele 8 of ILSTS42 and allele 6 of BM6026. The genetic map distances of the haplotypes were indicated as in (1c). The dashed line represents the comparisonwise *P*-value threshold level, whereas the solid line represents the chromosomewise *P*-value threshold level.

Table 2. Association between haplotype and growth traits in M1 line of *Bos taurus* from Beefbooster, Inc.

Haplotype[a]	Growth trait[b]	*P*-value[c]	Haplotype effect, kg[d]
BP1-4, BL23-3	BWT	0.0039**	–0.79 SD (3.54)
ILSTS42-4, BM6026-6	PWADG	0.0352*	+0.59 SD (0.06)
BM6062-6, BP1-3	PWADG	0.0281*	+0.77 SD (0.08)
ETH10-2, IGF1-2	PWADG	0.0259*	–0.41 SD (0.05)
IGF1-2, BM1819-5	PWADG	0.0053*	–0.46 SD (0.05)
BM1819-5, RM29-1	PWADG	0.0034**	–0.64 SD (0.07)
BM6026-6, BP1-4	ADGF	0.0055*	+0.62 SD (0.11)
RM500-4, BR2936-2	ADGF	0.0048**	+0.68 SD (0.12)
BR2936-2, BMS490-2	ADGF	0.0195*	+0.56 SD (0.10)
BMS490-2, ETH10-4	ADGF	0.0166*	+0.55 SD (0.10)

[a]The haplotypes were named by two alleles of a pair of loci. For example, haplotype BP1-4 and BL23-3 represents a segment of chromosome having allele 4 of BP1 and allele 3 of BL23.
[b]BTW = birth weight, PWADG = preweaning average daily gain, ADGF = average daily gain on feed.
[c]*and** indicate the *P*-values above the comparisonwise and chromosomewise thresholds, respectively.
[d]SD = standard deviation, + and – represent positive and negative effects, respectively. The actual haplotype effects in kilograms are shown in parentheses.

three growth traits. Table 2 lists the haplotypes that have a significant association with the growth traits above the comparisonwise threshold and chromosomewise threshold.

In total, 10 haplotypes showed significant associations with the growth traits at the comparisonwise threshold level (Table 2). The 10 haplotypes cover three chromosomal regions. The first chromosomal region is from ILSTS42 to BL23, a distance of about 28 cM. It is evident that the region has association with all three growth traits at the comparisonwise significance level, of which BP1-4, BL23-3 also showed an association with BTW at the chromosomewise threshold level. The second chromosomal region that affects ADGF spans from RM500 to ETH10, a distance of about 15 cM. The association between haplotype RM500-4, BR2936-2 and ADGF is significant at the chromosomewise threshold level. The third chromosomal region has a negative effect on PWADG; it spans from ETH10 to RM29 a distance of about 10 cM. Haplotype BM1819-5, RM29-1 exhibited a significant association with PWADG at the chromosomewise threshold level. Haplotype BP1-4, BL23-3 was the only haplotype associated with birth weight; animals with the haplotype tend to have a 0.79 SD lower birth weight. Five haplotypes showed significant associations with PWADG at the comparisonwise threshold: ILSTS42-4, BM6026-6; BM6062-6, BP1-3; ETH10-2, IGF1-2; IGF1-2, BM1819-5; and BM1819-5, RM29-1. Haplotypes ILSTS42-4, BM6026-6 and BM6062-6, BP1-3 have a positive effect on PWADG; animals with the two haplotypes tend to have higher PWADG (between 0.59 and 0.77 SD). The other three haplotypes ETH10-2, IGF1-2; IGF1-2, BM1819-5; and BM1819-5, RM29-1 however, have a negative effect on PWADG, animals with the haplotypes having lower PWADG (between 0.41 and 0.64 SD) Four haplotypes showed significant associations with ADGF at the comparisonwise threshold level. All four haplotypes have positive effects on ADGF, increasing the ADGF between 0.55 and 0.68 SD.

No significant haplotype × herd interaction was found in the current analysis. Among the correlation coefficients of five selected haplotypes (BM6026-6, BP1-4; BP1-4, BL23-3; RM500-4, BR2936-2; IGF1-2, BM1819-5; and BM1819-5, RM29-1), two were highly significantly different from zero at a *P*-value of 0.001 and one significantly different from zero at *P*-value of 0.05 (Table 3). Haplotype BP1-4, BL23-3 is positively correlated with the haplotype BM6026-6, BP1-4 with a coefficient of 0.2714. Haplotypes BM1819-5, RM29-1 and IGF1-2, BM1819-5 are also positively correlated, with a coefficient of 0.4482. The correlation coefficient between haplotypes RM500-4, BR2936-2 and IGF1-2, BM1819-5 was found to be significant and positive but at a *P*-value of 0.0351 and coefficient of 0.1613.

Common Haplotypes in the M3 Line and Their Associations with Growth Traits

On average, 5.6 alleles were detected for each locus of BTA5 in the M3 line, with a range of 2 to 11 alleles per locus. The definition of a haplotype in M3 line was the same as in the M1 line, which only considered adjacent loci along BTA5. The frequencies of the most common haplotype analyzed in M3 line ranged from 6.5% (haplotype BMS490-6, IGF1-1) to 49.0% (haplotype BM1819-5, RM29-1).

In total, nine haplotypes in the M3 line showed association with the growth traits at the comparisonwise threshold level. None of them, however, reached the stringent chromosomewise threshold level (Table 4, Figure 2). The nine haplotypes cover the same three chromosomal regions as identified in the M1 line. In the first chromosomal region of ILSTS42 to BL23, haplotype BP1-2, BL23-4 has a significant association with the birth weight at the threshold level of 0.0064, and animals with the haplotype have a lower birth weight of 0.95 SD. It was also found that other two haplotypes BM6026-6, BL1-2 and BP1-1, BL23-4 showed associations to some extent with PWADG and ADGF,

respectively, with *P*-values less than 0.10 but not reaching the comparisonwise threshold level (Figure 2). This suggests that the chromosomal region may affect all the growth traits in the M3 line as well. In the second chromosomal region of RM500 to ETH10, three haplotypes RM500-4, BR2936-1; BR2936-1, BMS490-6 and BMS490-6, IGF1-2 were found to have significant associations with the average daily gain on feed at the comparisonwise threshold level. The three haplotypes had a negative effect on ADGF, decreasing the ADGF between 0.48 and 0.78 SD. In the similar chromosomal regions, two haplotypes, BMS490-6, IGF1-1 and BMS490-4, IGF1-2, are significantly associated with the birth weight at the comparisonwise threshold level. The two are alternative haplotypes of the same chromosomal segment, with one having a positive effect of 0.96 SD on the birth weight (haplotype BMS490-6, IGF1-1) and the other a negative effect of 0.53 SD on the birth weight. In the third chromosomal region of ETH10 to RM29, three haplotypes IGF1-2, BM1819-1; IGF1-2, BM1819-3; and BM1819-1, RM29-1 showed significant associations with the preweaning average daily gain. Haplotypes IGF1-2, BM1819-1 and BM1819-1, RM29-1 have positive effects of 1.02 and 0.85 SD, respectively, on PWADG. The third haplotype IGF1-2, BM1819-3 is an alternative haplotype between IGF1 and BM1819 and has a negative effect on PWADG.

Discussion

The successful application of marker-assisted selection (MAS) in commercial animal populations will depend on a number of factors. Among these are the ability to identify the genes or closely linked markers to the genes underlying the QTL, the ability to test whether allelic variations at these loci are segregating in the population, and an understanding of how these genes interact with the environment or with other genes affecting economic traits. All this must be done in an efficient and cost-effective manner in order for the technology to be adopted in the livestock industries.

Identity by descent QTL mapping using haplotype sharing has been successfully demonstrated in humans (de Vries et al. 1996; Fallin et al. 2001) and cattle (Riquet et al. 1999). The method takes advantage of linkage disequilibrium in populations with limited outbreeding, in which common chromosome segments are shared by individuals in populations that originated from a few common founders. Thus, chromosome segments that house the QTL can be identified through direct haplotype comparison. The strategy of such fine mapping of QTL overcomes the limitation of interval-based QTL mapping, which requires large numbers of progeny of a single sire and which may be difficult or costly to implement in domestic animal species.

Haplotype-based mapping approaches have other advantages over interval-based QTL mapping. In the latter, a QTL is identified and mapped based on the cosegregation of a genetic marker and the QTL; thus, only markers at heterozygous loci are informative. The haplotype sharing mapping method; however, makes use of haplotypes that span at least two loci, thus, the markers of homozygous loci are still informative as long as the adjacent locus is heterozygous.

The feasibility of using haplotype mapping methods depends on the extent of the linkage disequilibrium. Farnir et al. (2000) reported that linkage disequilibrium in a Holstein-Friesian dairy cattle population extended over several tens of centimorgans. In our study, we also observed that some haplotypes between two adjacent markers have much higher frequencies than others in both the M1 and M3 lines. Such a phenomenon may be attributed to the introduction of a limited number of founders and artificial selection over generations, a common breeding practice for beef as well as dairy cattle. In a commercial breeding line, selection may play an even more important role in maintaining linkage disequilibrium, considering genetic drift and recombination for each generation. Selection that is in favor of desired traits increases the percentage of the haplotype housing the corresponding genes and thus makes IBD mapping using haplotype sharing even more feasible.

The M1 line has been developed as a maternal component of a commercial crossbreeding scheme. Selection is based on an index described by MacNeil and Newman (1994), along with independent culling levels specifying minimum and maximum BWT, minimum PWADG, and minimum ADGF in M1 individuals. Such a selection scheme may result in a higher frequency of some haplotypes that harbor genes for lower birth weight, higher

Table 3. Pearson correlation coefficients among haplotypes significantly associated with the growth traits at or close to the chromosomewise significance level[a] in M1 line of *Bos taurus* from Beefbooster, Inc.

Haplotype[b]	BP1-4, BL23-3	RM500-4, BR2936-2	IGF1-2, BM1819-5	BM1819-5, RM29-1
BM6026-6, BP1-4	0.2714 (0.0003***)	0.0049 (0.90484)	0.0286 (0.7057)	–0.0069 (0.9278)
BP1-4, BL23-3		0.0244 (0.7512)	0.0509 (0.5018)	–0.0691 (0.3619)
RM500-4, BR2936-2			0.1613 (0.0351*)	–0.0406 (0.5978)
IGF1-2, BM1819-5				0.4482 (0.0001***)

[a]The *P*-values for testing the hypothesis of a zero correlation coefficient are indicated in parentheses. * and *** indicate the *P*-values above the significant level of $P < 0.05$ and $P < 0.001$, respectively.

[b]The haplotypes were named by two alleles of a pair of loci. For example, haplotype BM6026-6 and BP1-4 represents a segment of chromosome having allele 6 of BM6026 and allele 4 of BP1.

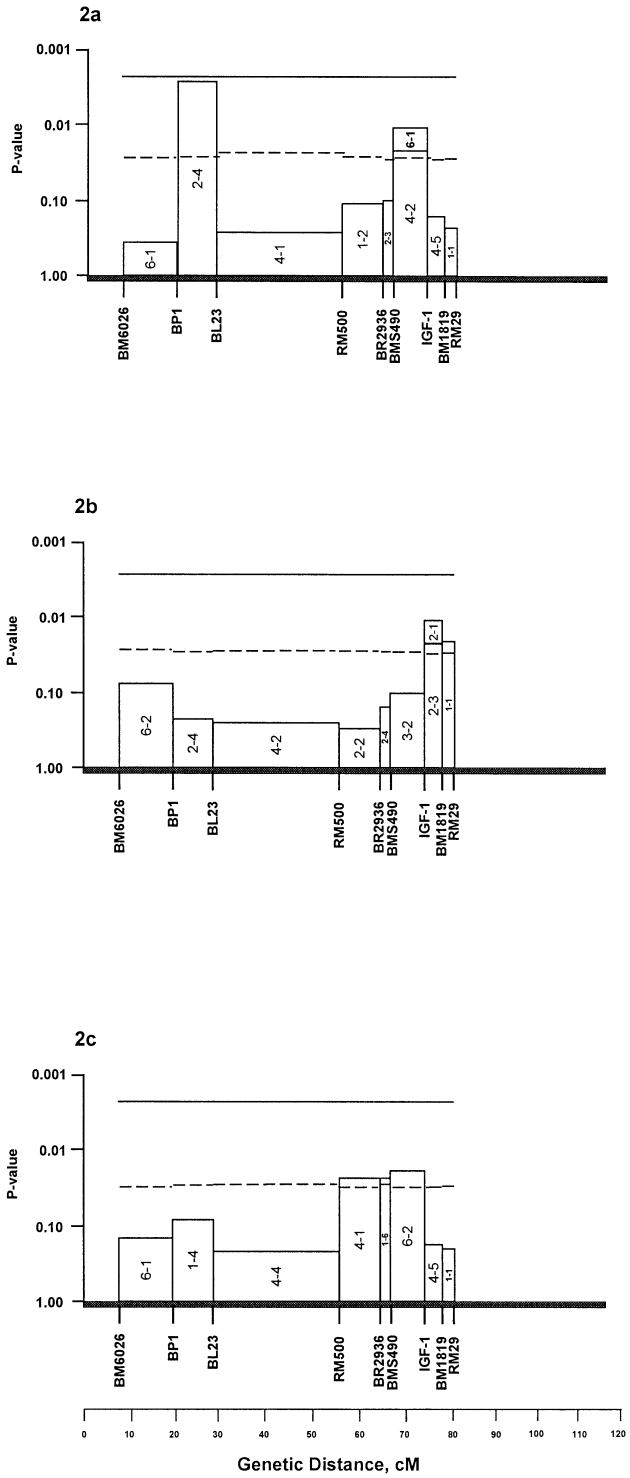

Figure 2. Haplotypes with the lowest *P*-values between two adjacent loci along BTA5 for birth weight (2a), preweaning average daily gain (2b), and average daily gain on feed (2c) in M3 line. Haplotypes were defined by two alleles of a pair of loci. For example, haplotype 6-1 of locus pair BM6026 and BP1 represents a segment of chromosome having allele 6 of BM6026 and allele 1 of BP1. The genetic map distances of the haplotypes were indicated as in (2c). The dashed line represents the comparisonwise *P*-value threshold level, whereas the solid line represents the chromosomewise *P*-value threshold level.

preweaning average daily gain and higher average daily gain on feed. We detected a haplotype (BP1-4, BL23-3) that was associated with lower birth weight at the chromosomewise significance level and another (BM1819-5, RM29-1) for lower preweaning average daily gain. The two haplotypes have frequencies of 10.2 and 27.8%, respectively. A third haplotype (RM500-4, BR2936-2) demonstrated a significant association with higher average daily gain on feed at the chromosomewise significance level and has a frequency of 18.8%. The relatively higher frequencies of haplotypes associated with lower birth weight and higher average daily gain on feed is in agreement with the selection scheme. The relatively higher frequency of the haplotype associated with lower preweaning average daily gain, however, seems at odds with the selection scheme. This may suggest genes in the region, associated with other traits in the index, are linked to the haplotype responsible for lower preweaning average daily gain. Considering that 18 traits were used in constructing the selection index (MacNeil and Newman, 1994), this would not be unexpected. This emphasizes the care that must be taken in implementing marker-assisted selection when only one or a few markers are considered. Selection on a marker may, as well, have negative effects on other traits due to pleiotropic effects of the gene or other genes closely linked to the marker affecting the other traits.

The M3 line has been developed to produce sires that minimize calving difficulty when mated to yearling heifers. Birth weight is therefore the major concern of selection, even though selection for lower preweaning gain and postweaning performance is also considered. Two haplotypes BP1-2, BL23-4 and BMS490-4, IGF1-2 were associated with lower birth weight at the comparisonwise threshold level. The two haplotypes have frequencies of 8.2 and 23.6%, respectively. A third haplotype (BMS490-6, IGF1-1), however, was associated with higher birth weight. The haplotype is an alternative allele of BMS490 and IGF1 and has a frequency of only 6.5%. The relatively higher frequency of haplotypes associated with lower birth weight is in agreement with the selection scheme in the M3 line. Of the three haplotypes associated with PWADG, one of them (IGF2, BM1819-3) has a negative effect on PWADG with a frequency of 11.1%, which is also in the agreement with the selection scheme in the M3 line. Two of them (IGF1-2, BM1819-1 and BM1819-1, RM29-1), however, have positive effects on PWADG, but the two haplotypes have lower frequencies of 6.6 and 6.8%, respectively. The three haplotypes associated with ADGF have negative effects on ADGF (Table 4), which seems at odds with the selection scheme in the M3 line. This may again suggest that selection for one growth trait, such as lower birth weight, has a strong influence on other growth traits.

Quantitative trait loci for birth weight have been mapped on bovine chromosome 5 in the region of 70 to 110 cM by Davis et al. (1998), and in the region of 50 to

Table 4. Association between haplotype and growth traits in M3 line of *Bos taurus* from Beefbooster, Inc.

Haplotype[a]	Growth trait[b]	*P*-value[c]	Haplotye effect, kg[d]
BP1-2, BL23-4	BWT	0.0064*	–0.95 SD (3.78)
BMS490-6, IGF1-1	BWT	0.0250*	+0.96 SD (3.82)
BMS490-4, IGF1-2	BTW	0.0345*	–0.53 SD (2.11)
IGF1-2, BM1819-1	PWADG	0.0093*	+1.02 SD (0.10)
IGF1-2, BM1819-3	PWADG	0.0419*	–0.51 SD (0.05)
BM1819-1, RM29-1	PWADG	0.0340*	+0.85 SD (0.09)
RM500-4, BR2936-1	ADGF	0.0469*	–0.71 SD (0.10)
BR2936-1, BMS490-6	ADGF	0.0469*	–0.78 SD (0.11)
BMS490-6, IGF1-2	ADGF	0.0316*	–0.48 SD (0.07)

[a]The haplotypes were named by two alleles of a pair of loci. For example, haplotype BP1-2 and BL23-4 represents a segment of chromosome having allele 2 of BP1 and allele 4 of BL23.
[b]BTW = birth weight, PWADG = preweaning average daily gain, ADGF = average daily gain on feed.
[c]* indicates the *P*-values above the comparisonwise threshold.
[d]SD = standard deviation, + and – represent positive and negative effect, respectively. The actual haplotype effects in kilograms are shown in parentheses.

85 cM by Stone et al. (1999). In our study, we identified a similar chromosomal region of 65 to 75 cM associated with the birth weight in the M3 line. Another QTL for growth (retail product yield) has been detected in the region of 60 to 95 cM of the chromosome by Casas et al. (2000). In this study, we detected two haplotypes significantly associated with growth traits at the chromosomewise threshold level in a similar region in the M1 line as well as in the M3 line. Haplotype RM500-4, BR2936-2, which is strongly associated with ADGF in the M1 line, is located in the region of 55 to 65 cM. Haplotype BM1819-5, RM29-1, having a strong effect on PWADG in the M1 line, is located in the area of 70 to 80 cM. In the M3 line, the chromosomal region between IGF1 to RM29 and chromosomal region between RM500 to IGF1 showed significant association with PWADG and ADGF, respectively, at the comparisonwise threshold level. Ge et al. (2001) found a mutation in the promoter region of the IGF-I gene, significantly associated with higher weight gain during the first 20 d after weaning and a slight dominance effect on postweaning gain. Whether this mutation is responsible for the effects seen in this current study is yet unclear.

Some differences in QTL location on BTA 5, however, were seen in this study when compared to other published results. We detected a region at 10 to 30 cM from the centromere that affected growth at all stages (BTW, PWADG, and ADGF) in the M1 line and in the M3 line as well. Whether there is one or more new QTL in this region is unclear at present. In this study, we tested the haplotype × herd interaction in the M1 line and found no significant effect. Such a result is not unexpected, given the fact that limited sample size and less-divergent environments (two herds) were used in this study. We also examined the correlation coefficients among five haplotypes (BM6026-6, BP1-4; BP1-4, BL23-3; RM500-4, BR2936-2; IGF1-2, BM1819-5; and BM1819-5, RM29-1) in the M1 line, representing five chromosomal locations showing association with the growth traits at or close to the chromosomewise significance level, and found two correlation coefficients were highly significantly different from zero at *P*-value of 0.001 and one significantly different from 0 at *P*-value of 0.05 (Table 3). Haplotype BP1-4, BL23-3, which has a negative effect on BTW at the chromosomewise significance level, is positively correlated with the haplotype BM6026-6, BP1-4; the haplotype has a positive effect on ADGF at the comparisonwise significance level. This result may reflect the effect of selection in the line, in which relatively lower birth weight and higher postweaning gain are preferred. The two haplotypes share one common allele, BP1-4, suggesting that one allele of the same gene may affect growth at different developmental stages or that two alleles of the gene are segregating in the population affecting the time of expression of the trait. Another highly significant correlation coefficient was found between haplotypes IGF1-2, BM1819-5 and BM1819-5, RM29-1. The two have negative effects on PWADG, are located adjacent to each other, and share one common allele. It is most likely that they represent only one gene in the area and selection of one haplotype could result in selection of the other haplotype as well. The correlation coefficient between haplotypes IGF1-2, BM1819-5 and RM500-4, BR2936-2 was also found to be positive and significant but at *P*-value of 0.0351. The haplotype IGF1-2, BM1819-5 has a negative effect on PWADG, and RM500-4, BR3926-2 has a positive effect on ADGF. The two haplotypes are located on the chromosome at a distance of about 10 cM apart, suggesting the weak correlation (r = 0.1613) may result from the linkage of the two haplotypes. Understanding the interaction between QTL and the interaction between a QTL and the environment provides good information for utilization of QTL in marker-assisted selection programs. With a larger sample size and more divergent environments, it should be possible to further test the gene actions underlying the haplotypes and their effects in different environments.

A complete dominance effect of the haplotype was assumed in this study, in which animals carrying one

copy of the haplotype and animals carrying two copies of the haplotype were treated the same. The main reason for a complete dominance assumption is that the number of animals carrying two copies of the same haplotype is very limited in both M1 and M3 lines, which prevents a valid test of different genetic models regarding the genetic effect between alleles of a locus, but should have little influence on the identification of haplotypes associated with the growth traits and estimation of the corresponding haplotype effect.

The chromosomal regions identified as having associations with the growth traits in the M1 line showed remarkable consistency with those identified in the M3 line (Figures 1 and 2), even though the haplotype phases were different (Tables 2 and 4). The difference in haplotype phase may due to different founders in M1 and M3 lines, given the fact that the M1 line was developed from an Angus base whereas the M3 line was developed from small cows of various breeds. The consistency of chromosomal regions associated with the growth traits in both lines strongly indicates the effectiveness of fine mapping QTL in commercial lines of livestock using the identical by descent haplotype sharing method. Thus, the fine mapped chromosomal regions of bovine chromosome 5 in this study should serve as a useful reference for further gene discovery research. The next step will be to initialize the search for the causative genes underlying the QTL regions through a positional candidate gene approach.

Implications

The identical by descent haplotype-based mapping used in this study has narrowed down the QTL regions on bovine chromosome 5 to around 10 cM when a chromosomewise significance level is applied. This demonstrates the feasibility of the haplotype sharing method in locating QTL in commercial herds of beef cattle. The results provide a reference for further positional candidate gene research and marker-assisted selection.

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